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ORIGINAL ARTICLE

Prevalence and clinical significance of potential drug-drug interactions in diabetic patients attended in a tertiary care outpatient center, Brazil

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Abstract The aim of this study is to investigate the prevalence of potential drug-drug interactions (PDDIs), as well as classifying them in relation to level of severity, scientific evidence, time of onset, and potential clinical impact in adult and older adult patients with diabetes mellitus 2 (DM2). This cross-sectional study was conducted in a tertiary care outpatient center. The consecutive sample was made up of 140 patients with DM2. The Anatomical-Therapeutic-Chemical Classification was used for classifying the classes of medications. The PDDIs were analyzed using the DRUG-REAX® system. The relationships between PDDI and the associated factors were ascertained using a multiple logistic regression model. The prevalence of total PDDI was 75 %, and the prevalence of major severity PDDI was 20.7 %. Simvastatin (30.8 %), captopril/enalapril (12.8 %), and oral anti-diabetics/insulin (12.8 %) were the medications which were most involved in the major PDDI, bringing relevant potential clinical impacts such as rhabdomyolysis, hyperkalemia, and important glycemic alterations. Polypharmacy was associated with PDDI (adjusted odds ratio = 10.46, 95 % confidence interval = 4.10–26.71). Diabetics were highly exposed to clinically significant PDDI. It is important that health professionals should be aware of the risks related to PDDI, so that measures may be implemented in order to assure safe care for the patient.

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Introduction

Chronic non-communicable diseases (NCDs) currently represent an important public health problem with high morbidity and mortality and significant economic repercussions. Although NCDs do not occur exclusively in older adults, it is anticipated that, with age, the individual will come to present some morbidity [1, 2]. Among these, one finds diabetes mellitus (DM), which, due to its chronic nature, requires long-term management. As a result, the treatment of DM aims to maintain good glycemic control, which generally prevents the appearance of the chronic complications which make up the principal causes of mortality, morbidity, and worsening of quality of life [3, 4].

As the disease progresses and with the presence of comorbidities such as dyslipidemia and systemic arterial hypertension (SAH), the patient may come to use complex antidiabetic treatments made up of three or more medications, as well as making use of other therapeutic agents for treating other comorbidities [5, 6]. Through this, the individual has greater exposure to the use of polypharmacy, that is, the use of five or more medications, contributing to the occurrence of drug interactions (DDIs) [7–9].

Drug interactions occur when two or more medications are used concomitantly and the actions of one medication (object, substrate) are altered by the presence of another (precipitant, interacting medication), causing an alteration of the clinical or pharmacological effect on the patient's response to the treatment [10, 11]. The present study considers the potential drug-drug interactions (PDDIs). This term refers to the possibility of a given medication altering the intensity of the

pharmacological effect of another medication used simultaneously by the patient [10–12].

Studies in different scenarios have indicated negative outcomes related to DDI, which can result in adverse events, a reduction or increase in the medications' therapeutic effects, an increase in the toxicity of medications, an increase in the health services' costs, failure of the treatment, and/or serious complications for the patient, including the risk of death [8, 9, 12–18].

One study undertaken in Nepal [19] with adult and older adult diabetic patients attended in tertiary healthcare identified a prevalence of PDDI of 52.5 %, of which 92.1 % were of moderate severity. The medications which contributed most to the risk of PDDI were those acting on the cardiovascular system (49.5 %), followed by oral antidiabetics (31.2 %). A study undertaken with diabetic and hypertensive older adults indicated a prevalence of 47.8 % of PDDI, with 93.2 % classified as moderate severity and 6.5 % as major. The medications which contributed most to PDDI in this scenario were acetylsalicylic acid (14.3 %), enalapril (12.6 %), glibenclamide (12.0 %), and digoxin (8.6 %) [15].

However, other studies directed towards evaluating the prevalence of PDDI, as well as its possible significant clinical implications in diabetic adult and older adult individuals, are scarce. In light of these considerations, this study aimed to investigate the prevalence of potential PDDIs, as well as classifying them in relation to level of severity, scientific evidence, time of onset, and potential clinical impact in adult and older adult patients with diabetes mellitus 2 (DM2).

Methods

Study design and setting

This cross-sectional study was conducted in an outpatient center specializing in DM, Arterial Hypertension and Obesity, at the Hospital de Clínicas, University of Campinas, Brazil. The service undertakes an average of 700 free attendances per year for adults and older adult patients, as it is part of the Unified Health System.

Sample selection and data collection

The consecutive sample was made up of 140 adult and older adult patients with DM2, receiving drug treatment with at least two medications, and who had been treated on an outpatient basis for a minimum of 12 months in the service. Data collection took place between May and October 2012. For extraction of the data, patient medical records were consulted, and an instrument was used which was made up of demographic-clinical variables and those related to the drug treatment.

Classification of the potential DDI

The present study considers the potential drug-drug interactions (PDDIs). This term refers to the possibility of a given medication altering the intensity of the pharmacological effect of another medication used simultaneously by the patient [10–12]. Only the PDDI related to major those that were quite severe were considered clinically significant due to the potential impact on the morbidity or mortality of the patients. The analysis of the PDDI was undertaken using the DRUG-REAX® system (Truven Health Products, 2015), which allows the identification of the PDDI according to severity, scientific evidence, time of onset and provides additional information such as potential clinical impact and clinical management [22].

The level of severity was categorized as follows: contraindicated, concomitant drug use is not recommended; major, interaction may be life-threatening and/or require medical intervention to reduce or prevent serious adverse effects; moderate, the interaction may result in aggravation of the patient's condition and/or require a change in the therapy; minor, the interaction would result in limited clinical effects and could include an increase in the frequency or severity of side effects but should generally not require any change in therapy; and unknown, interactions are unknown [22]. In terms of scientific evidence, the PDDIs were categorized as follows: excellent, controlled clinical studies have clearly established the existence of DDI; good, the documentation strongly suggests that there is an interaction, but no controlled clinical studies are available; fair, availability of documentation is poor, although pharmacological considerations exist regarding the interaction, or the documentation is good for a pharmacologically similar drug; and unknown, there is no evidence of such interactions [22]. For the time of onset, the PDDIs were classified as follows: rapid, onset expected within 24 h; delayed, onset not expected to occur within the first 24 h; and not specified, time not known [22].

Analysis of the data

The data collected were transferred to a Microsoft Excel 2010® Windows 8 spreadsheet, using double keying. The medications were classified by the Anatomical-Therapeutic-Chemical Classification—ATC, in level 1—main anatomical group [20]. The description of the qualitative variables was undertaken through the calculation of frequencies and percentages, and for the quantitative variables, measures of central tendency and dispersion were calculated. In order to study the association and the variables of sex, age range, number of drugs taken, body mass index (BMI) (normal, pre-obesity, and obesity), number of comorbidities, time since diagnosis, and HbA1c values with the variables of presence/absence of PDDI, simple logistic regression models were applied [21] and, subsequently, multiple models were constructed with

the stepwise criteria for selecting variables. The HbA1c values used in this study were based on a previous study [23], which demonstrated that HbA1c values between 7 and 8 % contribute to lower risks of mortality in diabetic patients. The results were presented through calculations of the raw and adjusted odds ratios. For all the analyses, a level of significance equal to 5 % was considered, and the SAS (Statistical Analysis System) statistical software, version 9.2, was used.

Results

Clinical-demographic profile

Over a 6-month period, 140 patients with a diagnosis of DM were included in this study. The distribution of these sociodemographic and clinical characteristics is presented in Table 1.

Therapeutic profile and potential drug interactions

The mean number of drugs used was 6.3 (SD 2.6). The majority of patients (79.3 %) were using five or more drugs. A total of 75 active substances were prescribed, with 364 pairs of PDDI being found: 39 (10.7 %) belonged to the group of major severity PDDI, 300 (82.4 %) belonged to the group of moderate severity PDDI, and 25 (6.9 %) to the group of minor PDDI. Contraindicated PDDIs were not found.

Among the 140 individuals, 105 were exposed to at least one PDDI, resulting in prevalence of 75.0 %. Among these patients, more than half (63.2 %) were exposed to between one and three PDDIs (mean of 2.6, SD 1.8). The prevalence of patients exposed to major PDDI was 20.7 % ($n = 29$), the case being that, in this group, 72.4 % were exposed to at least one major PDDI, 20.6 % to two major PDDIs, and 7 % to three major PDDIs. Table 2 presents the data referent to the 105 patients exposed to PDDI. In both the group of older adults and the group of adults, the moderate PDDIs were the most frequent (66.7 %), followed by the major PDDI (27.6 %).

Among the medications which contributed most to major severity PDDI, 50.0 % belonged to group C (cardiovascular system), followed by 17.8 % to group A (digestive system and metabolism) and 17.8 % to group N (nervous system). Simvastatin 30.8 %, captopril/enalapril 12.8 %, and oral antidiabetics/insulin 12.8 % were the drugs which were most involved in these events. In relation to the major PDDI, 86.9 % of the scientific evidence was classified as either excellent or good quality; 47.8 % was classified as delayed, that is, the onset was not expected to occur within the first 24 h (Table 3).

Statistically significant differences were not found in the multiple models between the variable presence/absence of PDDI with sex, age range, BMI, number of comorbidities, time since diagnosis, and HbA1c. In both univariate and multiple analyses, the number of drugs prescribed was associated with PDDI, with a growing risk among both patients who were not using five or more drugs and those who were doing so (OR = 10.46; CI 95 % 4.10–26.71) (Table 4).

Table 1 Demographic-clinical characteristics of patients with diabetes mellitus type 2, attended in a tertiary healthcare outpatient center

Demographic-clinical variables	Number	(%)
Sex		
Female	75	53.6
Male	65	46.4
Age in years		
Mean (SD)	60.5 (9.4)	–
Individuals <60 years	67	47.9
Individuals ≥60 years	73	52.1
BMI		
Mean (SD)	29.5 (6.1)	–
Comorbidities		
Systemic arterial hypertension	121	86.4
Dyslipidemia	93	66.4
Obesity	66	47.5
Peripheral vascular disease	38	27.3
Previous acute myocardial infarction	24	17.5
Angina	13	9.3
Cerebrovascular accident	06	4.3
HbA1C		
Mean (SD)	8.6 (1.9)	–
<7	33	23.6
≥7 and ≤8	31	22.1
>8 %	76	54.3
Fasting glycemia		
Mean (SD)	166.3 (69.3)	–

Discussion

The patients in the present investigation used a number of medications (6.3; SD 2.6) similar to that in other studies held in a tertiary healthcare outpatient center which included patients with DM2 in their samples [24–27].

Approximately 79 % of the patients made use of five or more medications. In the literature, the values for polypharmacy varied from 25.2 to 96.7 % [8, 15, 24, 25, 27, 28]. It is believed that this variation referent to the number of patients using five or more medications may be related to the level of care (primary or tertiary), to the associated morbidities, and to the study design.

In the present study, the prevalence of patients exposed to PDDI was 75 %. Rates of PDDI varying from 52.2 to 93.3 % have been described in patients receiving outpatient treatment in various specialties, including DM2 [19, 24, 25, 27].

Table 2 Distribution of patients with diabetes mellitus type 2 monitored in tertiary care, in relation to exposure to potential drug interactions, by severity

Severity	Number (%) of patients exposed to potential drug interactions[a]		
	Adults	Older adults	Total
Contraindicated	–	–	0 (0)
Major	11 (37.9)	18 (62.1)	29 (27.6)
Moderate	32 (45.7)	38 (54.3)	70 (66.7)
Minor	3 (50.0)	3 (50.0)	6 (5.7)
Total	46 (43.8)	59 (56.2)	105 (100.0)

[a] The patients exposed to more than one potential drug interaction were considered only once, that is, by the interaction with the greatest relevance

In this study, the prevalence of patients exposed to major severity PDDI was 20.7 %. This result is superior to the findings of a Mexican study which presented a prevalence of major PDDI of 3.8 %, in which only 29.5 % of the patients were diabetics [25]. This fact may be associated with the patients' differences in relation to the diagnoses and consequently, in relation to the drug treatment prescribed.

The prevalence of pairs of major severity PDDI was 10.7 % in the present study, this result falling within the values (3.67–17.6 %) present in other investigations with patients receiving outpatient treatment, which included DM2 [19, 24, 26, 27]. The major PDDI are considered clinically relevant, as it is important for health professionals to be aware of the risks related to the PDDI, so that measures may be implemented in order to ensure safe care for the patient.

The medications involved with the greatest frequency in major severity PDDI were simvastatin, captopril/enalapril, and oral antidiabetics/insulin, which is consistent with other studies which presented these combinations [9, 15]. More than half of the participants (58.6 %) had SAH and dyslipidemia,

Table 3 Frequency of pairs of clinically significant major severity potential drug interactions in prescriptions of patients with diabetes mellitus type 2 attended in a tertiary healthcare outpatient center

Drug A	Drug B	Frequency (%)	Potential clinical impact	Evidence	Time
Simvastatin	Amiodarone	10 (25.6)	↑ risk of rhabdomyolysis and myopathy	E	R
	Amlodipine			G	R
Captopril Enalapril	Spironolactone	5 (12.8)	Hyperkalemia	G	D
NPH insulin Insulin R Metformin Glibenclamide	Norfloxacin	4 (10.3)	Important glycemic alterations	E	R
Clopidogrel	Omeprazole	4 (10.3)	↓ clopidogrel efficacy and ↑ risk of thrombosis	E	R
	Amlodipine				NS
Simvastatin	Warfarin	2 (5.1)	↑ risk of rhabdomyolysis and of bleeding	E	D
Captopril	Losartan	2 (5.1)	Hypotension, syncope, kidney failure	E	NS
Amiodarone	Carvedilol Propranolol	2 (5.1)	Hypotension, bradycardia, and cardiac arrest	E	R
Digoxin	Amiodarone Spironolactone	2 (5.1)	Nausea, vomiting and cardiac arrhythmia	E G	D
Carbamazepine	Fluoxetine	2 (5.1)	↑ risk of toxicity of the carbamazepine	G	NS
Atenolol	Diltiazem	1 (2.6)	Hypotension, bradycardia, atrioventricular conduction disturbances	G	R
Atenolol	Clonidine	1 (2.6)	↑ risk of sinus bradycardia	F	NS
Amitriptyline	Fluoxetine	1 (2.6)	Prolongation of the QT interval, torsades de pointes, cardiac arrest	G	NS
Metformin	Topiramate	1 (2.6)	↑ risk of lactic acidosis	F	NS
Hydrochlorothiazide	Lithium	1 (2.6)	↑ of the concentration of the lithium (weakness, tremors, excessive thirst and confusion)	G	NS
Allopurinol	Enalapril	1 (2.6)	Hypersensitivity reactions	F	R

↑ increase, ↓ decrease, *F* fair, *G* good, *E* excellent, *R* rapid, *D* delayed, *NS* not specified

Table 4 Factors associated with the potential drug interactions in patients with diabetes mellitus type 2 attended in a tertiary healthcare outpatient center

Variable	PDDI				Raw odds ratio (C.I. 95 %)	*p* value	Adjusted odds ratio (C.I. 95 %)*	*p* value
	No		Yes					
	n	%	*n*	%				
Sex								
Male	14	21.54	51	78.46	1.00 (ref)	0.3797		
Female	21	28.00	54	72.00	0.71 (0.33; 1.54)			
Age range (years)								
<60	21	31.34	46	68.66	1.00 (ref)	0.0994		
≥60	14	19.18	59	80.82	1.92 (0.88; 4.19)			
BMI								
Normal	12	37.50	20	62.50	1.00 (ref)	0.1385		
Pre-obesity	12	25.00	36	75.00	1.75 (0.66; 4.07)			
Obesity	11	18.33	49	81.67	2.67 (1.00; 7.05)			
No. of drugs								
<5	19	65.52	10	34.48	1.00 (ref)	< 0.0001	1.00 (ref)	<0.0001*
≥5	16	14.41	95	85.59	11.28 (4.45; 28.62)		10.46 (4.10; 26.71)	
No. of comorbidities								
≤2	25	35.21	46	64.79	1.00 (ref)	0.0058		
>2	10	14.49	59	85.51	3.21 (1.40; 7.34)			
Time since diagnosis								
≤60 months	9	21.95	32	78.05	1.00 (ref)	0.5924		
>60 months	26	26.26	73	73.74	0.79 (0.33; 1.87)			
HbA1c (%)								
<7	7	21.2235	26	78.78	1.00 (ref)	0.6389		
≥7 and ≤8	7	22.58	24	77.42	0.82 (0.24; 2.80)			
>8	21	27.63	55	72.37	0.63 (0.23; 1.75)			

associated with DM2. This may explain the greater occurrence of PDDI with cardiovascular system drugs, as well as with medications for controlling dyslipidemia.

In general, the statins are used for preventing cardiac events and are well established for patients with dyslipidemia [29]; accordingly, simvastatin is a medication which is widely prescribed for the patient with DM2, given that dyslipidemia is a frequently associated comorbidity. Combined with amlodipine or amiodarone, there is an increase in the risk for myopathy and rhabdomyolysis; the risk of rhabdomyolysis and bleeding also increases with the use of warfarin [30–32]. In this way, these PDDIs represent a risk to health and consequently require interventions from the multi-professional team for preventing serious adverse effects. These patients must be monitored and guided in relation to signs and symptoms of the disease.

The risk for hyperkalemia occurred with the combined use of captopril/enalapril with spirinolactone in 12.8 % of the PDDI. This phenomenon is usually asymptomatic, and the greatest risk is the occurrence of arrhythmias. One study indicated that the combination of angiotensin-converting enzyme inhibitors with spironolactone gave rise to hyperkalemia, posing serious risks to the patients; 76 % of the patients presented electrocardiographic changes compatible with hyperkalemia (T tenting, QRS widening, or PR prolongation), with two patients dying in the emergency room [33].

One study revealed that the combination of these drugs was also associated with a significant increase in the risk of patients being transferred to the intensive care unit (ICU) or dying. The risk of death after 2 days from the detection of hyperkalemia was 5.3 times greater than in patients who were not exposed to PDDI, which led to this adverse event [34]. The combination, therefore, must be carefully evaluated with regard to the risk and benefit for each patient.

Other important combinations found in this study were for norfloxacin with insulin or oral antidiabetics (10.3 %). According to the literature, the main effect of combining these drugs is severe hypoglycemia [35, 36]. It is important to emphasize that the patient who maintains rigor in metabolic control already presents a risk for hypoglycemia and, associated with the combination of these drugs, the risks increase and may expose the patient to risks of death.

The combination of clopidogrel with omeprazole or amlodipine was also among the most common in this study (10.3 %). The USA's Food and Drug Administration (FDA) issued an alert regarding the interaction of clopidogrel with omeprazole [37]. Omeprazole reduces the antiplatelet effect of clopidogrel by approximately 50.0 %. However, it seems that omeprazole is rapidly eliminated, and the PDDI may be attenuated when the clopidogrel and the omeprazole are administered with an interval of 12 h. In some studies, the concomitant use of calcium channel blockers and clopidogrel was associated with a reduction of the action of the clopidogrel [38, 39]. In other studies, however, this hypothesis was not confirmed, and in these cases, there is no evidence that calcium channel blockers may reduce the efficacy of the treatment using clopidogrel [40, 41]. For this, it is necessary to undertake studies which better seek scientific evidence.

The use of five or more drugs was significantly associated with PDDI. Polypharmacy is a factor which is well documented in the literature as a factor associated with PDDI, independent of the disease investigated, country or place of care, and health treatment [8, 9, 12–18]. The polypharmacy recorded in this study is expected for this population, given that these individuals present an increased risk for cardiovascular diseases, such as SAH, dyslipidemias, and abnormalities related to coagulation. The higher the number of comorbidities, the greater the chances of co-administration of various drugs for the control of DM and its associated comorbidities.

The present study's results confirm the risk to the safety of patients with chronic diseases who are subjected to polypharmacy. The professional team needs to exercise continuous surveillance in relation to identifying signs/symptoms and possible alterations in laboratory examinations which result from PDDI and to review drug treatment so as to propose changes when possible. Furthermore, the professional must advise patients and their family members with the aim of reinforcing the early identification and treatment of these possible clinical implications. It falls to the health system to implement warning systems in the electronic prescriptions, with the aim of detecting and preventing prescriptions with problems, as well as providing databases on PDDI which allow PDDI to be tracked in real time. The use of warning systems for categorizing PDDI by severity, in certain care scenarios, has improved the acceptance of the clinical recommendations, such that specific medications should not be prescribed simultaneously [42].

Among this study's limitations, one finds the selection of the consecutive sample, which may prejudice its external validity. The PDDIs were established through the evaluation of the medical prescriptions of patients treated on an outpatient basis and were not compared with the actual clinical impact caused to the patient, which indicates a field for future investigations. On the other hand, this study, undertaken with diabetic patients, appears to be one of the first to investigate PDDI in this population, which contributes to shedding light on those PDDIs which are clinically significant, and provides data for assisting in developing warning systems for treatment of persons with diabetes, this being a group with greater vulnerability, due to the presence of comorbidities, the increase of possibilities of complications, and the use of complex polypharmacy.

Conclusion

Diabetic patients were exposed to clinically significant PDDI, the case being that polypharmacy increased the chances for PDDI. The most frequent potential clinical impacts were rhabdomyolysis, hyperkalemia, and important glycemic alterations. It is important for health professionals to know the risks related to the PDDI, so that measures may be implemented in order to ensure safe care for the patient. Changing the therapeutic scheme must be discussed within the multiprofessional team and undertaken where possible.

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Conflicts of interest The authors declare that they have no competing interests.

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